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**Declarations under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

**Published:**
— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2005/009990 A1

(54) Title: ARIPIPRAZOLE CRYSTALLINE FORMS

(57) Abstract: The present invention provides novel crystalline forms of aripiprazole and processes for their preparation.

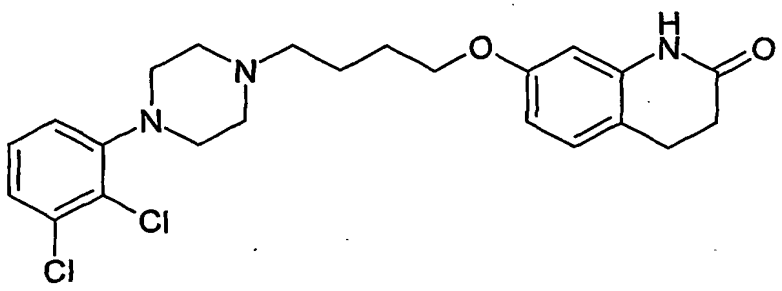
# ARIPIPRAZOLE CRYSTALLINE FORMS

## FIELD OF THE INVENTION

The present invention provides novel crystalline forms of aripiprazole and processes for their preparation.

## BACKGROUND OF THE INVENTION

Aripiprazole of formula (1):



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or 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone and its salts are useful for treating schizophrenia and their therapeutic uses were disclosed in US 5,006,528.

Processes for the preparation of aripiprazole and its salts were described in US 5,006,528. Various crystalline forms of aripiprazole and its hydrates were disclosed in WO 03/026659, Japanese Unexamined Patent Publication No. 191256/1990 and 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996).

We have discovered a novel crystalline form of aripiprazole, aripiprazole methanolate and aripiprazole ethylene dichloride solvate. The novel crystalline form of aripiprazole is non hygroscopic, do not have the tendency to convert to other forms and suitable for pharmaceutical preparations.

The methanolate and ethylene dichloride solvate are non-hygroscopic, obtainable in pure form and can be converted to crystalline forms of aripiprazole and aripiprazole hydrates.

Therefore, the solvates are useful as intermediates for preparing pure aripiprazole or aripiprazole hydrates in any crystalline form.

Thus, one object of the present invention is to provide stable, non-hygroscopic crystalline form of aripiprazole, process for preparing this form and pharmaceutical compositions containing it.

Another object of the present invention is to provide aripiprazole methanolate and aripiprazole ethylenedichloride solvate and process for preparing the solvates; and use of these solvates to prepare other forms of aripiprazole.

## DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of aripiprazole. The crystalline form is designated as aripiprazole form III and typical form III x-ray powder diffraction spectrum of aripiprazole form III is shown in figure 1.

Aripiprazole form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 8.8, 11.2, 11.4, 11.9, 13.6, 14.4, 15.0, 15.9, 16.4, 17.8, 18.7, 20.4, 20.8, 21.4, 22.2, 23.5, 25.0, 25.9 and 26.5 degrees.

In accordance with the present invention, there is provided a process for preparation of the aripiprazole form III comprising the steps of:

a) preparing a solution of aripiprazole in a mixture of methyl tert-butyl ether, acetonitrile and tetrahydrofuran; and
b) isolating aripiprazole form III from the solution.

Aripiprazole used in the process can be in any of the crystalline forms. Aripiprazole solvate or hydrate form can also be used in the process to produce aripiprazole form III.

The solution of aripiprazole is usually prepared at elevated temperature, preferably at reflux temperature and then the solution is cooled preferably to $0^0$C to $30^0$C, more preferably to $15^0$C to $30^0$C. The precipitated form III crystals are collected by filtration or centrifugation.

In accordance with the present invention, there is provided aripiprazole methanolate. The content of methanol is between about 2 to 6% of the weight of aripiprazole methanolate. Aripiprazole methanolate typically shows a crystalline

form, which is designated as aripiprazole methanolate form IV and typical form IV x-ray powder diffraction spectrum of aripiprazole methanolate form IV is shown in figure 2.

Aripiprazole methanolate form IV is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 9.8, 11.0, 11.8, 12.1, 12.6, 13.6, 17.4, 18.8, 20.1, 23.3, 24.6, 25.0, 25.9, 27.2, 28.4, 29.3, 30.1 and 31.5 degrees.

In accordance with the present invention, there is provided a process for preparation of the aripiprazole methanolate form IV comprising the steps of:

a) preparing a solution of aripiprazole in a mixture of methanol and tetrahydrofuran; and

b) isolating aripiprazole methanolate form IV from the solution.

The solution of aripiprazole is usually prepared at elevated temperature, preferably at reflux temperature and then the solution is cooled preferably to $0^0$C to $30^0$C. The precipitated form IV crystals are collected by filtration or centrifugation.

Aripiprazole methanolate can be used to prepare aripiprazole forms by crystallizing from the appropriate solvent system. Thus, for example aripiprazole form III can be prepared by preparing a solution of aripiprazole methanolate in a mixture of methyl tert-butyl ether, acetonitrile and tetrahydrofuran and isolating aripiprazole form III from the solution.

In accordance with the present invention, there is provided aripiprazole ethylenedichloride solvate. The content of ethylenedichloride is between about 15 to 40% of the weight of aripiprazole ethylenedichloride solvate. Aripiprazole ethylenedichloride solvate typically shows a crystalline form, which is designated as aripiprazole ethylenedichloride solvate form V and the typical form V x-ray powder diffraction spectrum of aripiprazole ethylenedichloride solvate form V is shown in figure 3.

Aripiprazole ethylenedichloride solvate form V is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 10.7, 17.6, 17.8, 20.6, 22.1, 23.4, 24.7 and 26.4 degrees.

In accordance with the present invention, there is provided a process for preparation of the Aripiprazole ethylenedichloride solvate form V comprising the steps of:

a) preparing a solution of aripiprazole in ethylenedichloride and

b) isolating aripiprazole ethylenedichloride solvate form V from the solution.

The solution of aripiprazole is usually prepared at elevated temperature, preferably at reflux temperature and then the solution is cooled preferably to $0^0$C to $30^0$C. The precipitated form V crystals are collected by filtration or centrifugation.

Aripiprazole aripiprazole ethylenedichloride solvate can be used to prepare aripiprazole forms by crystallizing from the appropriate solvent system. Thus, for example aripiprazole form III can be prepared by preparing a solution of aripiprazole ethylenedichloride in a mixture of methyl tert-butyl ether, acetonitrile and tetrahydrofuran and isolating aripiprazole form III from the solution.

In accordance with the present invention, there is provided a pharmaceutical composition comprising aripiprazole form III and a pharmaceutically acceptable carrier or diluent.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of aripiprazole form III.

Figure 2 is a x-ray powder diffraction spectrum of aripiprazole methanolate form IV.

Figure 3 is a x-ray powder diffraction spectrum of aripiprazole ethylenedichloride solvate form V.

x-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a copper-K$\alpha$ radiation.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

### Example 1

Aripiprazole (3 gm) is mixed with methyl tert-butyl ether (25 ml) and heated to reflux temperature. Then acetonitrile (45 ml) and tetrahydrofuran (25 ml) are added to the mixture and heated to about $55^0$C to form a clear solution. The solution is slowly cooled to $25^0$C, stirred for 1 hour at about $25^0$C and the

precipitated crystals are collected by filtration to give 2 gm of aripiprazole form III.

Example 2

Aripiprazole (3 gm), obtained by a known method is mixed with methanol (30 ml) and heated to reflux temperature. Then tetrahydrofuran (25 ml) is added at the same temperature to form a clear solution. The solution is slowly cooled to about 25°C, stirred for 1 hour at about 25°C and the separated crystals are collected by filtration to give 2.9 gm of aripiprazole methanolate form IV.

Example 3

Example 1 is repeated using aripiprazole methanolate obtained as in example 2 instead of aripiprazole to give aripiprazole form III.

Example 4

Aripiprazole (3 gm) is mixed with ethylenedichloride (30 ml) and heated to 50°C to form a clear solution. The solution is slowly cooled to 25°C, stirred for 1 hour at about 25°C and the separated crystals are collected by filtration to give 2.5 gm of aripiprazole ethylenedichloride solvate form V.

Example 5

Example 1 is repeated using aripiprazole ethylenedichloride solvate obtained as in example 4 instead of aripiprazole to give aripiprazole form III.

We claim:

1) A crystalline aripiprazole form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 8.8, 11.2, 11.4, 11.9, 13.6, 14.4, 15.0, 15.9, 16.4, 17.8, 18.7, 20.4, 20.8, 21.4, 22.2, 23.5, 25.0, 25.9 and 26.5 degrees.
2) A crystalline aripiprazole form III as defined in claim 1, further characterized by an x-ray powder diffraction spectrum as in figure 1.
3) A process for preparation of aripiprazole form III as defined in claim 1, which comprises the steps of:
a) preparing a solution of aripiprazole in a mixture of methyl tert-butyl ether, acetonitrile and tetrahydrofuran; and
b) isolating aripiprazole form III from the solution.
4) Aripiprazole methanolate.
5) Aripiprazole methanolate of claim 4, wherein methanol content is between about 2 to 6% of the weight of aripiprazole methanolate.
6) A crystalline aripiprazole methanolate form IV, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 9.8, 11.0, 11.8, 12.1, 12.6, 13.6, 17.4, 18.8, 20.1, 23.3, 24.6, 25.0, 25.9, 27.2, 28.4, 29.3, 30.1 and 31.5 degrees.
7) A crystalline aripiprazole methanolate form IV as defined in claim 6, further characterized by an x-ray powder diffraction spectrum as in figure 2.
8) A process for preparation of aripiprazole methanolate as defined in claim 4, which comprises the steps of:
a) preparing a solution of aripiprazole in a mixture of methanol and tetrahydrofuran; and
b) isolating aripiprazole methanolate from the solution.
9) A process according to claim 8, wherein the product obtained is aripiprazole methanolate.
10) A process according to claim 3, wherein aripiprazole is used in the form of Aripiprazole methanolate.
11) Aripiprazole ethylenedichloride solvate.
12) Aripiprazole ethylenedichloride solvate of claim 11, wherein ethylenedichloride content is between about 15 to 40% of the weight of aripiprazole ethylenedichloride solvate.

13) A crystalline aripiprazole ethylenedichloride solvate form V, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 10.7, 17.6, 17.8, 20.6, 22.1, 23.4, 24.7 and 26.4 degrees.

14) A crystalline aripiprazole ethylenedichloride solvate form V as defined in claim 13, further characterized by an x-ray powder diffraction spectrum as in figure 3.

15) A process for preparation of aripiprazole ethylenedichloride solvate as defined in claim 11, which comprises the steps of:

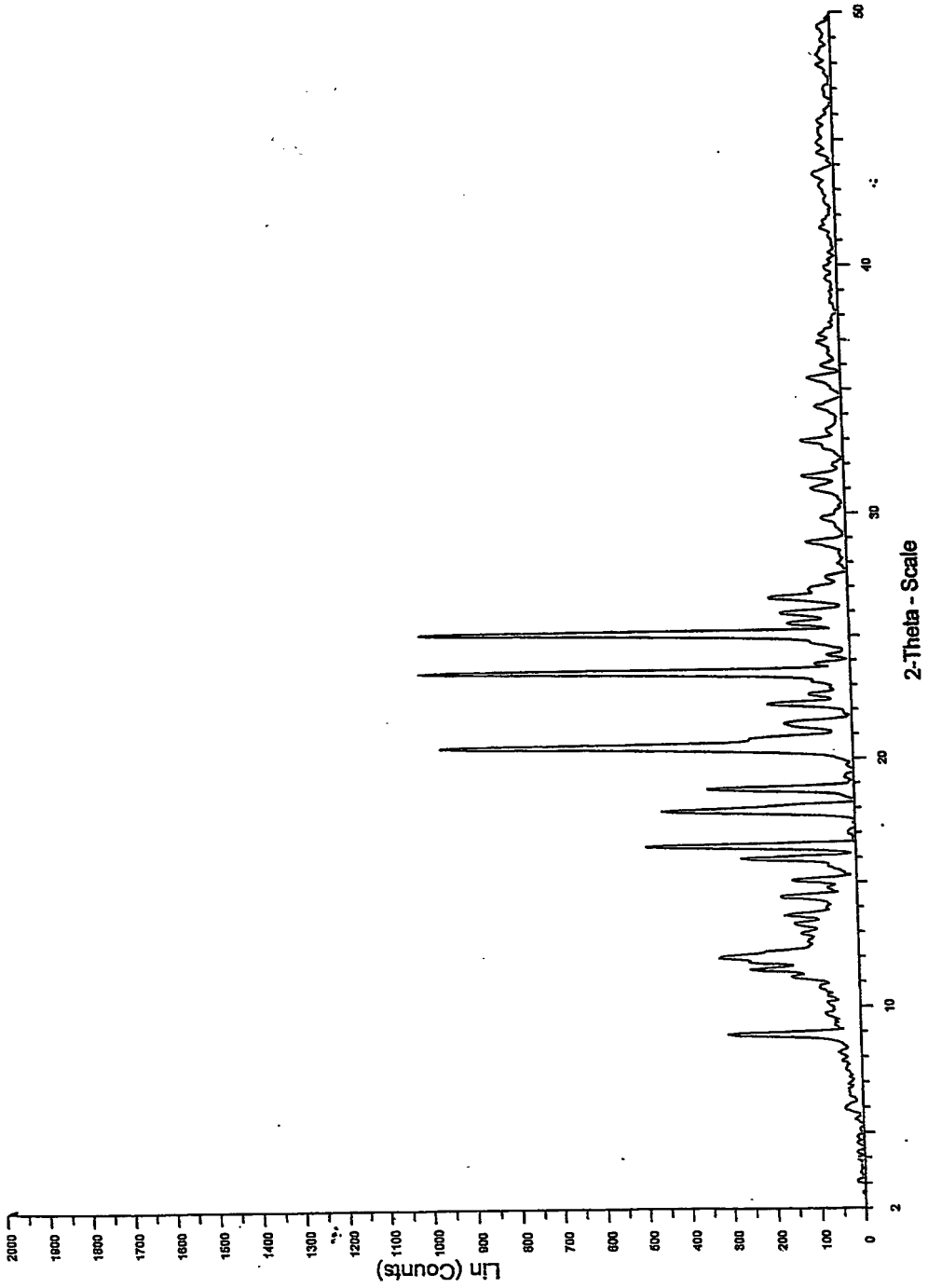
a) preparing a solution of aripiprazole in ethylenedichloride; and

b) isolating aripiprazole ethylenedichloride solvate from the solution.

16) A process according to claim 15, wherein the product obtained is aripiprazole ethylenedichloride form V.

17) A process according to claim 3, wherein aripiprazole used is in the form of Aripiprazole ethylenedichloride.

18) A pharmaceutical composition comprising aripiprazole form III of claim 1 and a pharmaceutically acceptable carrier or diluent.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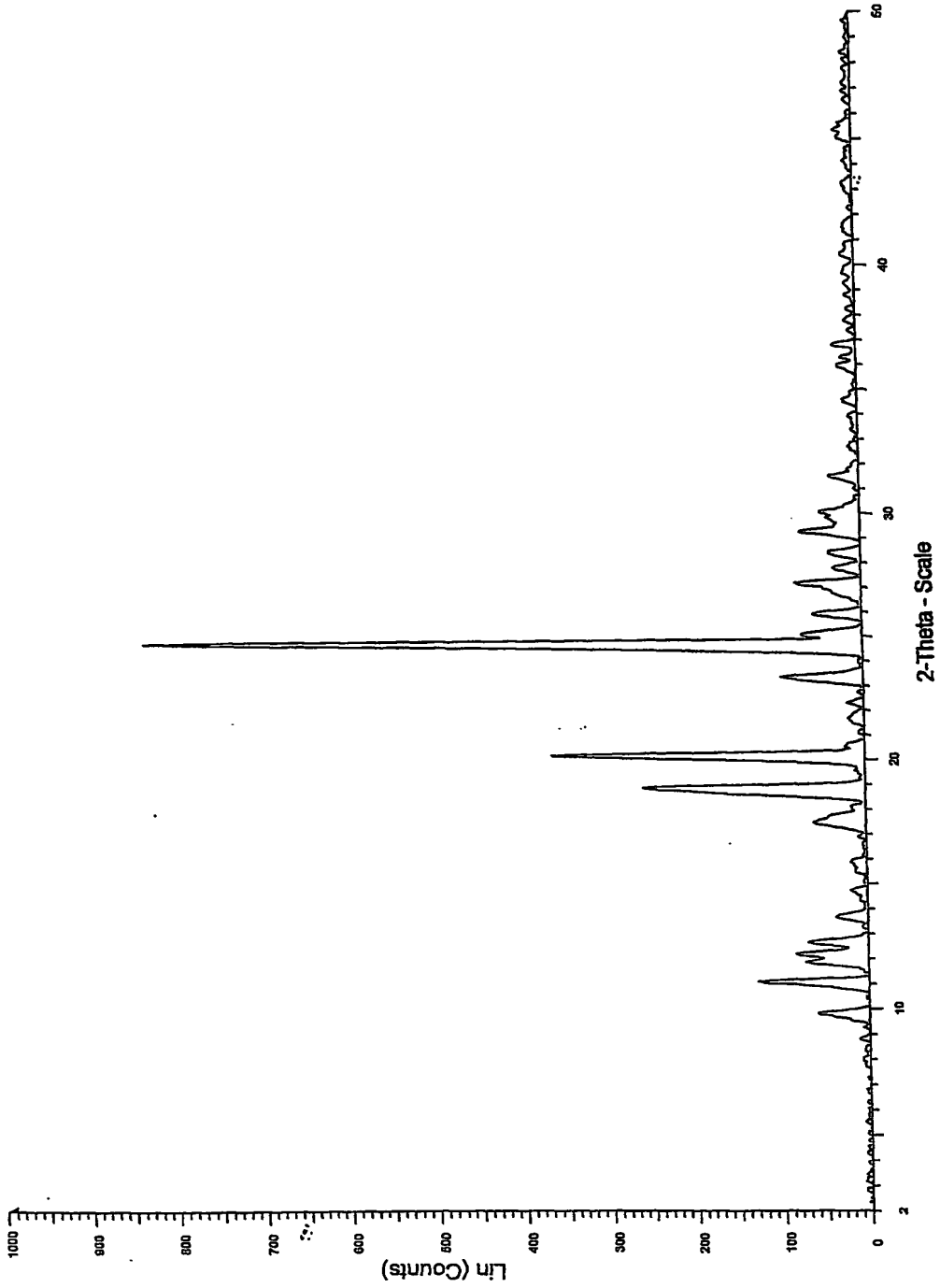
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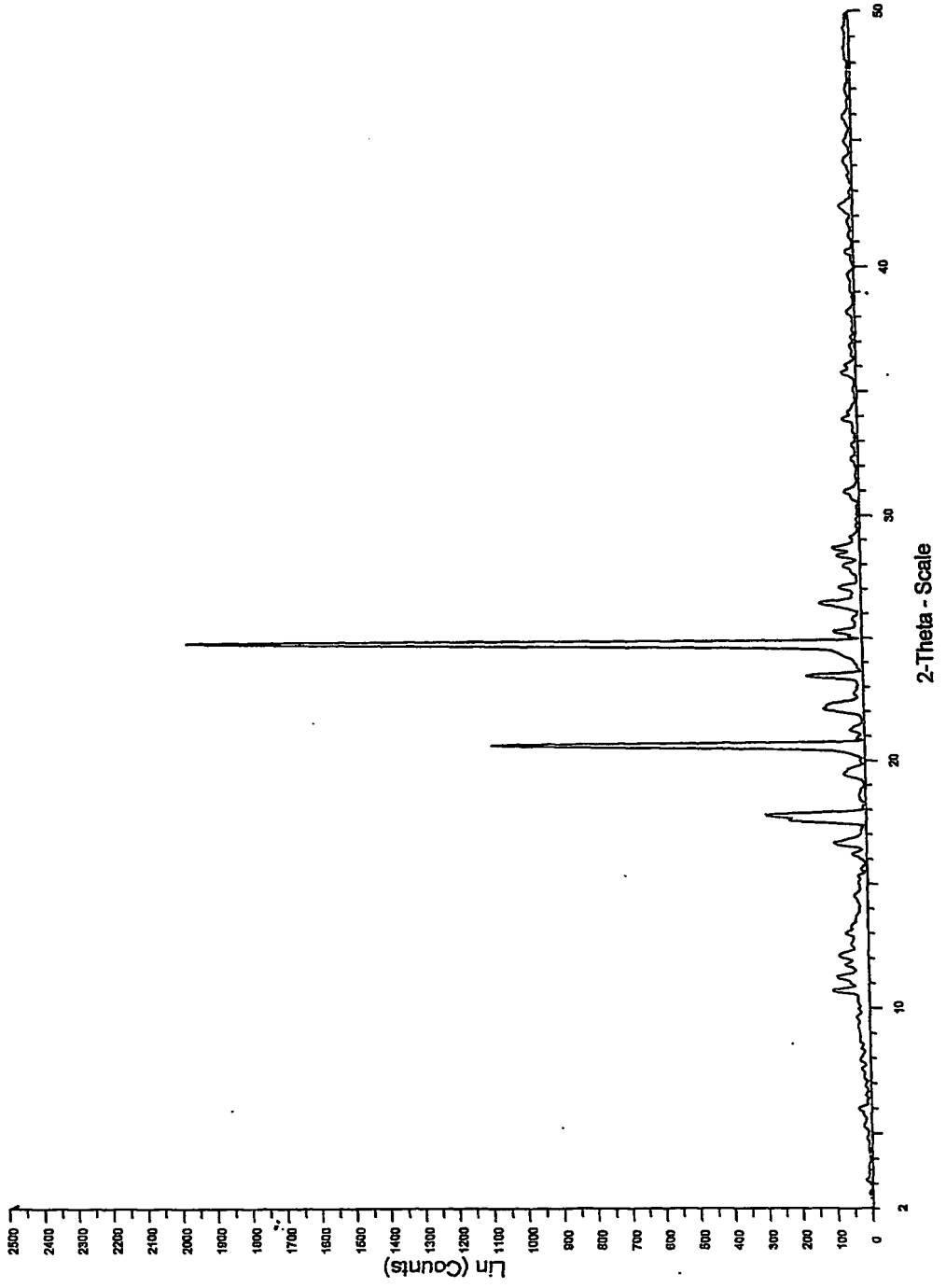
Lin (Counts)
2-Theta - Scale

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00251-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 401/12, A61K 31/497

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, EPODOC, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2003/026659 A1 (Otsuka Pharmaceutical Co., LTD) 3 April 2003 (03.04.2003) *the whole document, figure 15.* | 1, 3, 10, 17, 18 |
| A | *the whole document.* | 4, 6, 8, 9, 11, 13, 15, 16 |
| A | EP 0367141 A2 (Otsuka Pharmaceutical CO., LTD) 9 May 1990 (09.05.1990) *the whole document.* | 1, 3, 4, 6, 8-11, 13, 15-18 |
| Â | US 5006528 A (Oshiro et al.) 9 April 1991 (09.04.1991) *the whole document.* | 1, 3, 4, 6, 8-11,13, 15-18 |

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 March 2004 (05.03.2004) | 3 May 2004 (03.05.2004) |
| Name and mailing adress of the ISA/AT<br>Austrian Patent Office<br>Dresdner Straße 87, A-1200 Vienna<br>Facsimile No. 1/53424/535 | Authorized officer<br>GÖRNER W.<br><br>Telephone No. 1/53424/0 |

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00251-0

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | Satoshi Aoki et al. "Study on Crystal Transformation of Aripiprazol" in The Fourth Japan - Korea Symposium On Separation Technology, Organized by The Society of Separation Process Enigneers, Japan, and The Diviosn of Separation Technology, The Korean Institute of Chemical Engineers, October 1996, CR 119, pp. 937-940 *results.* | 1, 3, 4, 6, 8-11,13, 15-18 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00251-0

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2, 5, 7, 12 and 14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

-)No search was conducted for claims 2, 7 and 14 since they refer to figures only.
-)Since the content of solvent in crystals is important for their structure, percentage ranges of crystal-solvents are not sufficient for the characterization of crystalline forms as claimed in claims 5 and 12, hence no search was carried out for these claims.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Supplemental sheet

Remarks

The search was carried out on the assumption that the crystalline forms of the compounds in claims 1, 6 and 13 do not contain any impurities, although the description of the application does not contain data to confirm this.
However, for proper characterization of the (polymorphic) crystalline form of a compound by powder x-ray diffraction data, the purity of the (polymorphic) crystal should be confirmed by elementary analysis or NMR data and described in the invention to rule out the possibility that peaks used for characterization are generated by impurities.
Furthermore, the amount of measured compound should be described to make sure that comparable results are presented.

In claims 3, 8 and 15 the parameters for the process steps b) should be described clearly and concisely in technical terms, since process steps of isolation of the compounds have great influence on the (crystalline) form of the compound. The search was carried out in consideration of the techniques used and mentioned in the examples section of the description only (i.e. cooling).

# INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/IN 03/00251-0

| Patent document cited in search report | Publication date | Patent family member(s) | | | Publication date |
|---|---|---|---|---|---|
| | | | | none | |
| EP A 367141 | | BR | A | 1100204 | 2000-08-01 |
| | | HK | A | 1002706 | 1998-09-11 |
| | | KR | B | 138529 | 1998-05-15 |
| | | JP | A | 10045718 | 1998-02-17 |
| | | JP | A | 10045717 | 1998-02-17 |
| | | DK | A | 539789 | 1990-05-01 |
| US A 5006528 | | BR | A | 1100204 | 2000-08-01 |
| | | HK | A | 1002706 | 1998-09-11 |
| | | KR | B | 138529 | 1998-05-15 |
| | | JP | A | 10045718 | 1998-02-17 |
| | | JP | A | 10045717 | 1998-02-17 |
| | | DK | A | 539789 | 1990-05-01 |
| | | | | none | |
| WO A 20030266 59 | | | | | |